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ω-Alkenyl-α-Methoxy-Benzyllithiums : Original Synthesis and Reactivity

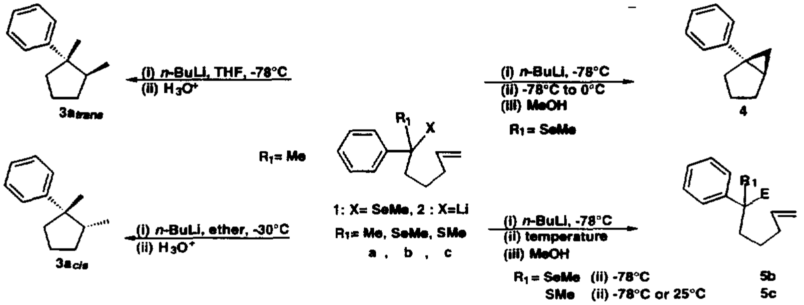
Alain Krief* and Jamal Bousbaa

Department of Chemistry, Facultés Universitaires Notre-Dame de la Paix, 61 rue de Bruxelles B-5000, NAMUR (Belgium)

Abstract : 1-Methoxy-benzyllithiums bearing suitably positioned C,C double bonds possess a high propensity to produce a five or a six membered cycle by carbocyclisation reaction. The reaction proceeds completely stereoselectively and produces a five membered cycle possessing the *cis*-stereochemistry between the methoxy and the adjacent methyl group. © 1997 Published by Elsevier Science Ltd.

We have already described that benzyllithiums with built-in C,C double bonds **2**, readily available from the corresponding methylseleno derivatives **1** possess a high propensity to cyclise to cyclopentyl methyllithiums. We also found that the structure and the stereochemistry of the compounds (**3**-**5**) produced after methanolysis, depends upon the nature of the starting material and in some cases upon the solvent used (Scheme 1). Thus 2-phenyl-2-hept-6-enyllithium **2a** bearing a methyl substituent on the carbanion produces 1-phenyl-1,2-dimethyl cyclopentane **3** possessing the *cis*- or the *trans*- stereochemistry between the two methyl groups whether the reaction is conducted in THF (-78°C) or ether (-30°C) (Scheme 1).[1a] At the contrary, **2b** in which the "benzylic" methyl group has been replaced by a methylseleno substituent delivers the bicyclo [3.1.0] hexane derivative **4** if the reaction is performed in THF at 0°C or produces 1-methylseleno-1-phenyl-5-hexene **5b** when performed in THF at -78°C and quenched at that temperature (Scheme 1).[1b] Surprisingly however, the analogous compound **1c**, bearing a methylthio substituent on the carbanionic center affords 1-methylthio-1-phenyl-5-hexene **5c** whatever are the conditions used (Scheme 1).[1c]

Scheme 1



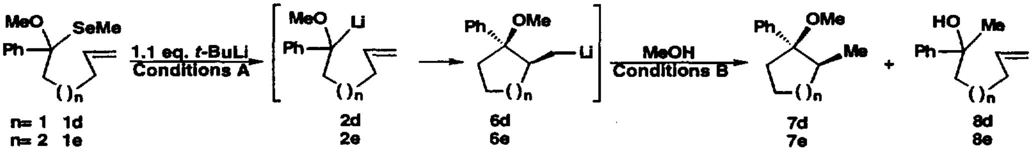
Dedicated Professor D. Seebach at the occasion of his 60 th Birthday with great appreciation for his fundamental contribution to Organic Chemistry .

In that context, it was interesting to study the behavior of related 1-methoxy-1-methylseleno-1-phenyl-hex-5-ene **1d** and 1-methoxy-1-methylseleno-1-phenyl-hept-6-ene **1e** towards alkyllithiums.[2]

We now report that **1d** is efficiently cleaved by *t*-butyllithium in solvents of a wide range of polarity and basicity (THF, ether, pentane) to produce, after methanolysis, 1-methoxy-2-methyl-1-phenyl-cyclopentane **7d** in very good yield and as a single stereoisomer. Cyclisation of the intermediate 1-methoxy-1-phenyl-1-hex-5-enyllithium **2d** is quite rapid in THF (-78°C, 0.5h; Scheme 2, entry a), slower in ether (-40°C, 5h; Scheme 2, entry b)[3] and even slower in pentane (20°C, 48h; Scheme 2, entry c).

This reaction has been also successfully extended to the homologous 1-methoxy-1-methylseleno-1-phenyl-hept-6-ene **1e** which delivers the six membered cycle **7e** with complete stereocontrol[4] but besides small amounts of the methyl phenyl carbinol **8e** resulting from the Wittig rearrangement[5] of the intermediate 1-methoxy-1-phenyl-1-hept-6-enyllithium **2e** (Scheme 2, entries e,f).

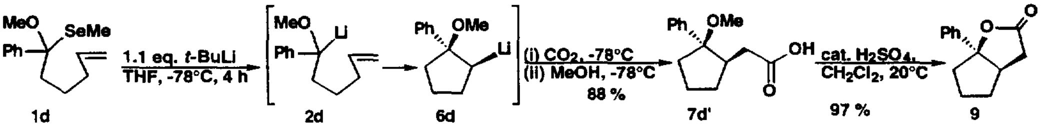
Scheme 2



entry	n	Conditions A	Conditions B	Product	Yield in 7 %	Product	Yield in 8 %
a	1	THF, -78°C, 0.5 h	MeOH, -78°C	7 d	81	8 d	0
b	1	Et_2O, -40°C, 5 h	MeOH, -40°C	7 d	74	8 d	0
c	1	Pentane, 20°C, 48 h	MeOH, +20°C	7 d	92	8 d	0
d	1	Pentane, 2 eq. TMEDA, 20°C, 48 h	MeOH, +20°C	7 d	87	8 d	0
e	2	THF, -78°C, 8 h then -78°C to 20°C	MeOH, +20°C	7 e	61	8 e	30
f	2	pentane, 20°C, 168 h	MeOH, +20°C	7 e	64	8 e	15

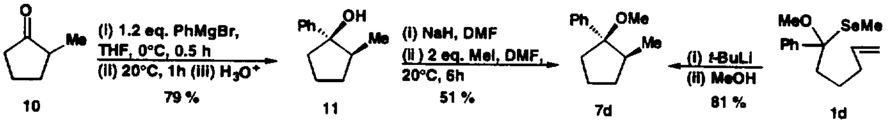
Trapping the reaction mixture obtained from **1d** and *t*-butyllithium with carbon dioxide instead of methanol leads, after acid hydrolysis, to the expected carboxylic acid **7d'** (Scheme 3). This not only unambiguously demonstrates that **6d** is still present in the medium after the carbocyclisation is completed, but also allows the efficient synthesis of the bicyclic lactone **9** on further reaction with an acid catalyst (cat. H_2SO_4, CH_2Cl_2, 20°C, 1h, 97 % yield, Scheme 3).

Scheme 3



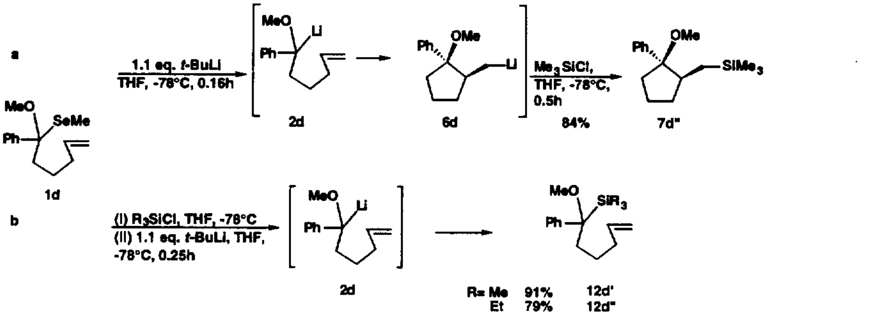
Although the above mentioned transformation does not prove the stereochemistry of **7d** or **7d'**,[6] comparison of **7d** with an authentic sample,[7] prepared from 2-methyl cyclopentanone **10** on sequential reaction with phenyl magnesium bromide and methyl iodide (Scheme 4), unambiguously shows that the methoxy and the methyl groups possess a *cis* relationship. This high stereocontrol of the cyclisation, observed in all the solvents used, is probably due to the squeezing of the lithium cation, in the transition state, between the methoxy group and the C,C double bond.

Scheme 4



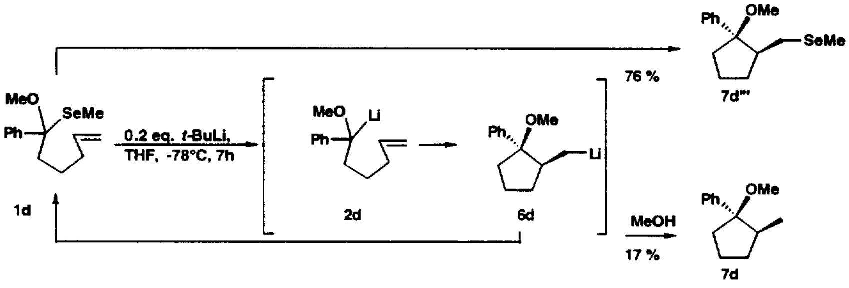
The cyclisation of 1-methoxy-1-phenyl-1-hex-5-enyllithium **2d** seems to be more rapid than that of analogous compounds bearing a seleno- **2b** or a thio- **2c** substituent on the carbanionic center (Scheme 1) and resembles more that of derivative **2a** which possesses a methyl group there. For example, we have not been able to trapp the benzyllithium **2d** prior its cyclisation to **6d** when the reaction between **1d** and *t*-butyllithium is carried out at -78°C and quenched at that temperature with chlorotrimethylsilane (Scheme 5, entry a). Interestingly, however, this is efficiently achieved if the cleavage of the C,Se bond is carried out in the presence of chlorotrimethylsilane (Scheme 5, b). The least reactive ethyltrichlorosilane behaves similarly (Scheme 5, entry b).

Scheme 5



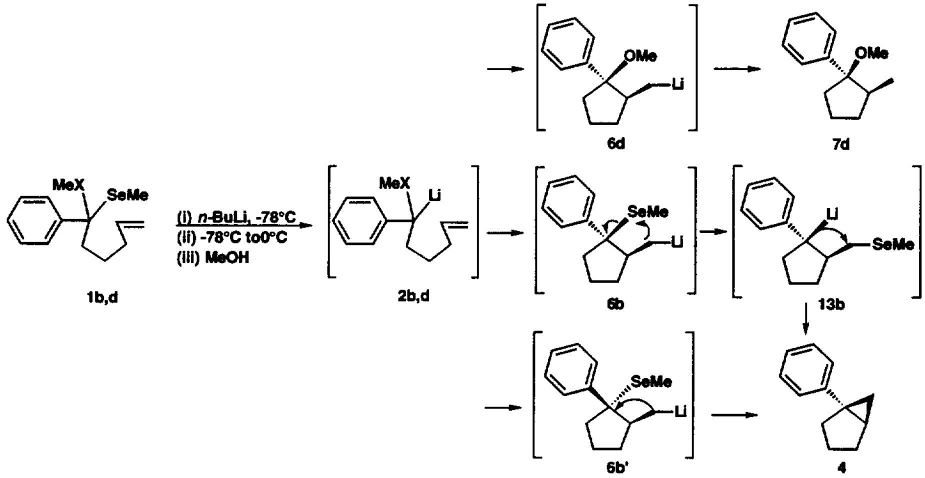
Finally, we have found that the carbocyclisation, leading to the isomeric 1-methoxy-2(methylselenomethyl)-1-phenyl cyclopentane derivative **7d'''**, can be achieved on reaction of **1d** with 20% of the stoichiometric amount of *t*-butyllithium (0.2 eq., THF, -78°C, 7h, Scheme 6). *t*-Butyllithium is rapidly consumed on reaction with 0.2 equivalent of **1d** to provide the same amount of **2d** leading finally to **6d**. Then **6d** takes the relay to cleave the C,Se bond of **1d** producing at the same time, **7d'''** and **2d** and this cycle goes on till all the starting material **1d** has been reacted. At the end, **1d** has been transformed to **7d'''**, besides 17% of **6d** (corresponding to the amount of *t*-butyllithium used in the process), which produces **7d** on further methanolysis.

Scheme 6



The results just disclosed let us to reconsider the "rationale" we previously described from the related methylseleno derivative **1b** which leads to the bicyclic derivative **4** (Scheme 7).[1b] The discrepancy between the behavior of **1b**, in which the intermediate **6b** further cyclises to **4**, and that of **6d** which remains unreactive could be due to (i) a better leaving group ability of the methylseleno- compared to the methoxy- group or to (ii) a different stereochemical relationship between the heteroatomic moiety and the CH_2Li group (**6b'** with the favorable *anti*-arrangement instead of **6b** or **6d** with the unfavorable *syn* -arrangement for the substitution reaction leading to the bicyclic derivative **4**). We can also suspect that **6b** isomerises, via an intramolecular heteroatom/Li exchange, to the novel benzyllithium **13b**, which has the proper arrangement to cyclise to **4**. This reaction is well known in selenium chemistry (Se/Li exchange)[8] but does not occur with oxygen compounds. We are currently working in that field.

Scheme 7



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1. (a) Krief, A.; Barbeaux, P. *J. Chem. Soc. Chem. Commun.* **1987**,*16*, 1214 (b) Krief, A.; Barbeaux, P. *Tetrahedron Lett.* **1991**, *32*, 417 (c) Krief, A.; Kenda, B.; Barbeaux, P. *Tetrahedron Lett.* **1991**, *32*, 2509.
2. (a) These compounds were easily prepared from 1-methoxy-1-methylseleno-toluene by metallation followed by alkylation of the intermediate 1-methoxy-1-methylseleno-benzylpotassium with 5-bromo-1-pentene and 6-bromo-1-hexene ((i) KDA, THF, -78°C, 1h (ii) $Br-(CH_2)n-CH=CH_2$, THF, -78°C, 0.5h; -78°C to 20°C : n= 1 89%; n= 2 84%).[2b] (b) Krief, A.; Bousbaa, J. *Tetrahedron Lett.* **1997**, *38*, 0000.
3. **2b** and **2c** do not cyclise under these conditions (see above, Scheme 1).[1d,c]
4. The stereochemistry of **7e** has not yet been determined.
5. Tomooka, K.; Nakai, T. *J. Synth Org. Chem. Jpn* **1996**, 54, 1000 (b) Nakai, T.; Mikami, K. in "*Organic Reaction*" **1994**, *46*, 106 Paquette, L. A. *ed.* John Wily & Sons, Chichester (c) Marshall, J.A. in "*Comprehensive Organic Synthesis* "**1991**, *Vol 3*, 975, Trost, B.; Fleming, I.; Pattenden, G. Pergamon Press, Oxford.
6. The reaction probably proceeds via an S_N1 type mechanism.
7. Ashby, E. C.; E.C.; Laemmle, J. T.*Chem. Rev.* **1975**, *75*, 521.
8. For a related example see Krief, A.; Barbeaux, P.; Guittet E. *Synlett* **1990**, 509.

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